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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,135	10/18/2006	Amar Lulla	PAC/23225 US (4137-00600)	8688

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EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,135	LULLA ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33 and 53* is/are pending in the application.

4a) Of the above claim(s) *9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-33,53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments, filed July 9, 2010, have been fully considered but they are not deemed to be fully persuasive. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

Response to Arguments

2. Applicant's arguments with respect to the pending claims have been considered but are moot in view of the new ground(s) of rejection.

Election/Restrictions

3. Based on the election of alendronic acid and the teachings of the newly applied reference, Adamaski et al. (WO 01/85176), claims 4 – 8 are no longer withdrawn from consideration and are found to be obvious variants of the elected species based on the teachings of this document.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1 – 8, 11 – 22, 25 - 32 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Katdare et al. (WO 95/29679) in view Adamski et al. (WO 01/85176)

Katdare et al. discloses forming a powder blend of active ingredient with diluent that is wet granulate (p 2, ln 15 – 20). Following wet granulation with an aqueous

solution, the dried granules can be combined with additional excipients, such as the disintegrant croscarmellose sodium and the lubricant magnesium stearate (p 5, ln 1 – 22). Preferred diluents include lactose and the carbohydrate alcohol mannitol (p 5, ln 32 – 33). Sodium lauryl sulfate can also be used as a lubricant (p 6, ln 11). Tablets are the preferred form of the pharmaceutical composition (p 7, last line). The bisphosphonic acid generally comprise about 0.5% to 25% by weight of the pharmaceutical formulation; the lactose [diluent] is about 30 – 70% by weight; 30 – 50% MCC [diluent]; 0.1 – 2% by weight magnesium stearate and about 0.5 – 2% of disintegrant such as croscarmellose sodium (p 8, ln 3 – 9).

Katdare et al. does not explicit disclose formulation with carbohydrate alcohols or formulations that do not include lactose.

Adamski et al teaches alendronic acid and the monosodium salt trihydrate, which is the active ingredient in FOSAMAX®, can be formulated with excipients such as microcrystalline cellulose (MCC), anhydrous lactose, croscarmellose sodium and magnesium stearate (p 1, ln 11 – 20). Lactose can generate formulation incompatibilities with primary or secondary amine, enhanced by the presence of water, that decrease the therapeutic value of the drug (p 2, ln 5 – 19). While a dry formulation process eliminates some of these problems, instability during storage especially in warm or damp remains (p 2, ln 26 – p 3, ln 9). The use of a carbohydrate alcohol, preferably D-mannitol, provides the internal formulation structure with uniformity of dose and required release rate with high stability of the final product. Tablets containing 6% sodium alendronate trihydrate, 1.5% magnesium stearate, 79% mannitol, crosslinked

and non-crosslinked polyvinylpyrrolidone, the lubricants sodium lauryl sulfate and magnesium stearate and 5% starch were prepared (p 10, ln 5 – 17).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to replace the lactose diluent of the formulation of Katdare et al. with a carbohydrate alcohol such as mannitol. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Adamski et al. disclose that lactose in conjunction with moisture, either during formulation or storage, generate chemical incompatibilities due to the amine group of alendronic acid that decreases the therapeutic value of the tablet over time and Katdare et al. disclose both lactose and mannitol as possible diluents. Replacement of lactose to eliminate these incompatibilities would yield formulations that do not contain lactose and includes granules of alendronic acid, mannitol and the diluent MCC with polyvinylpyrrolidone present as a binder. Magnesium stearate and/or sodium lauryl sulfate can be used as lubricants and the formulations of Adamski et al. use starch. The weight percentages of the various ingredients overlap with the ranges of the instant claims and overlapping range are *prima facie* obvious (see MPEP 2144.05). By including the disintegrant in the granules rather than outside the granules in the tablet formulation, not only will the tablet as a whole break up upon action of the disintegrant to individual granules containing active agent but the granules themselves with the active ingredient will also disintegrate.

8. Claims 1 – 8, 11 – 33 and 53 rejected under 35 U.S.C. 103(a) as being unpatentable over Katdare et al. and Adamski et al. as applied to claims 1 – 8, 11 – 22, 25 - 32 and 53 above, and further in view of Flash-Ner-Barak et al. (WO 2002/00204).

As discussed in greater detail above, Katdare et al. and Adamski et al. disclose wet granulated formulations of sodium trihydrate alendronate in which the lactose is replaced by a carbohydrate alcohol such as mannitol to reduced incompatibilities between the primary amine of alendronic acid and lactose which are exacerbated by water, either during formulation or storage after formulation.

Neither reference discloses the inclusion of 5% to 20% of a disintegrant such as sodium starch glycolate or capsule formulations.

Flash-Ner-Barak et al. discloses that when formulating a tablet or capsule, the other excipients present in rapidly expanding pharmaceutical composition are determined, in part, by whether a tablet or capsule is being formulated (p 9, ¶3). Flash-Ner-Barak et al. also discloses that the inventive composition includes a superdisintegrant, disintegrants which swell upon contact with water, such as sodium starch glycolate or cross-linked sodium carboxyl methyl cellulose (croscarmellose sodium; p 6, ¶ 3). The swelling of the dosage form provides a dosage form that remains in the stomach for an extended period of time and over time, particles of the dosage form degrade or erode away and enter the small intestine (p 8, ¶ 2), providing a delayed release of the active ingredient to the upper GI tract where alendronate is best absorbed (p 4, ¶ 4). The amount of superdisintegrant can vary from about 10% to about 75% by weight (p 7, ¶ 3).

It would have been obvious to one of ordinary skill in the art to prepare a dosage form as taught by Katdare et al. and Adamski et al. using alendronic acid, no lactose, MCC and mannitol which exhibits excellent stability of the active ingredient over time, and to use the superdisintegrant sodium starch glycolate in a tablet or capsule dosage form. The superdisintegrant – croscarmellose sodium as used in Katdare et al. and Adamski et al. or sodium starch glycolate, taught by Flash-Ner-Barak et al., allow for a dosage form which swells in the stomach and allows for the delayed release of the active ingredient to the upper GI tract for better absorption of the active ingredient over time. Flash-Ner-Barak et al. discloses that the formulation can be in the form of tablets of capsules and some patients can have difficulty swallowing tablets and find it easier to swallow capsules, so the formulation could instead be used to make a capsule rather than a tablet.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nissa M Westerberg/
Examiner, Art Unit 1618